

Research Progress of Liposomes in the Field of Anti-Tumor Therapy

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Abstract: Liposomes, as an efficient nanoscale drug carrier, hold significant advantages in antitumor therapy. The unique bilayer structure of phospholipids enables liposomes to simultaneously encapsulate both lipophilic and hydrophilic drugs, while also possessing good biocompatibility and low immunogenicity. Through passive or active targeting mechanisms, liposomes can precisely deliver drugs to tumor tissues, thereby significantly enhancing therapeutic efficacy and reducing systemic adverse reactions. This paper summarizes and reviews the preparation, composition, classification of liposomes, and their applications in diseases such as breast cancer, lung cancer, and glioma. It also highlights that the development of special functional liposomes, such as long-circulating liposomes, thermosensitive liposomes, pH-sensitive liposomes, and ligand-targeted liposomes, has further improved the precision and efficacy of drug delivery, bringing new breakthroughs and hope for antitumor treatment.

Keywords: Liposomes, Antitumor, Drug Delivery System

1. Introduction

The key to treating malignant tumors lies in the precise inhibition of tumor cells while protecting normal cells. Traditional therapies such as chemotherapy, radiotherapy, and surgery are effective, but often associated with resistance and adverse effects. Combination drug strategies have emerged, and nanomaterials have become an important drug delivery system to improve the efficiency of cancer treatment due to their small size and unique functions [1]. Liposomes are the first to be applied to clinical cancer treatment due to their advantages of easy preparation, good biocompatibility, encapsulation of multiple types of drugs, low adverse reactions and high targeting. Liposomes can be used as carriers to selectively locate drugs to target tissues, target organs, target cells or intracellular structures through systemic or local administration through passive and active targeting mechanisms, so as to exert their therapeutic effects on diseases [2].

At present, 16 original liposomal drugs have been approved by the FDA or EMA, with more than 1,000 liposomal products are in clinical trials. However, liposomes also exhibit physical and chemical instability, precluding terminal sterilization. Instead, they typically rely on filtration sterilization and aseptic techniques. Additionally, the phenomenon of "accelerated blood clearance" after multiple injections further underscores the necessity for ongoing liposome research. Researchers need to continue to explore ways to improve its performance, and expand its application [3].

2. Basic Introduction to Liposomes

2.1. Basic Composition

The phospholipid molecules of lipid nanomaterials are composed of hydrophilic heads and hydrophobic tails. When forming liposomes, the hydrophilic heads are located on the exterior of the bilayer while the hydrophobic tails point inward. This configuration enables the loading of both lipophilic and hydrophilic drugs, with hydrophilic drugs residing within the particle's core and lipophilic drugs incorporated into lipid bilayer. Due to the bilayer structure resembling a biofilm, liposomes have good biocompatibility and immune responses in smaller organisms [4].

2.2. Preparation Method

2.2.1. Film Dispersion Method

The thin-film dispersion method is a simple and commonly used technique for preparing multi-chamber or large single-chamber liposomes. In this method, lipid materials are dissolved in an organic solvent such as chloroform, and the organic solvent is removed to form a thin film by rotary evaporation under reduced pressure, and then a buffer is added to hydrate it to obtain multilayer liposomes (MLV). Liposome homogenization techniques, such as ultrasound and extrusion, can yield small unilamellar vesicles (SUVs) or large unilamellar vesicles (LUVs) with consistent particle size [5].

In sonication, the MLVs prepared by the thin-film dispersion method are sonicated to achieve a particle size of approximately 250 nm. The duration and mode of ultrasound significantly impact the final liposome particle size. Water-bath ultrasound is suitable for large or low-concentration samples, with the water temperature needing to be monitored to prevent drug instability. Probe-based ultrasound is suitable for viscous or highly concentrated samples with high energy and good results.

The extrusion method involves passing the liposome suspension, prepared by the thin-film dispersion method and ultrasonic treatment, through a polycarbonate film perforated by lasers with varying pore sizes. This process yields a large number of small and uniform LUVs or SUVs with consistent particle sizes.

2.2.2. Reverse Evaporation Method

The reverse phase evaporation method involves dissolving the liposome membrane materials in an organic solvent, mixing them with an aqueous solvent, and forming a water-in-oil emulsion-like liposome suspension by ultrasound in a water bath, and obtain the liposome suspension after evaporation to remove the organic solvent under reduced pressure. Liposomes produced by this method can be used to encapsulate nucleic acid drugs, and can also be used to encapsulate small molecule chemical drugs, supplemented by extrusion to obtain SUVs with uniform particle size [6].

The improved reverse evaporation method first dissolves the liposome membrane material in an organic solvent, evaporates it under reduced pressure to form a thin film. Isopropyl ether or another organic solvent is then added to re-dissolve the film, followed by the addition of an aqueous solvent to create a water-in-oil-like liposome suspension. The particle size is homogenized by ultrasonic and extrusion methods to form a monolayer of liposomes. Finally, the organic solvent is evaporated under reduced pressure to obtain a drug-loaded SUV liposome suspension [7].

3. Classification of Liposomes

3.1. Ordinary Liposomes

Ordinary liposomes are highly susceptible to uptake by the reticuloendothelial system (RES), leading to the preferential accumulation of encapsulated drugs in the liver and spleen. This phenomenon results in a passive targeting effect. Although this property can be advantageous in certain therapeutic contexts, it may significantly limit the application of ordinary liposomes when precise drug delivery to other specific sites is required.

3.2. Long-cycle Liposomes

Polyethylene glycol (PEG) is an amphiphilic and linear polymer that extends the hydrophilic end of liposomes, significantly increasing steric hindrance. This structural design effectively prevents the adhesion and aggregation of plasma opsonogenic proteins and liposomes, thereby avoiding rapid uptake by the reticuloendothelial system (RES). Modification of liposomes by PEG can significantly prolong their time in the systemic circulation, increase the aggregation of drugs at the lesion site, and reduce the toxicity and adverse reactions of immune organs [8].

Liver macrophages are mostly responsible for removing colloidal particles from the bloodstream in many species, including humans. This rapid and primary clearance mechanism poses significant challenges in redirecting sufficient amounts of intravenously granular drugs to other parts of the body to exert therapeutic effects. However, researchers have discovered that the creation of long-circulating nanoparticles offers a previously unheard-of chance for both drug delivery to locations other than liver macrophages and controlled drug release inside the vasculature. By avoiding hepatic macrophages, and carefully manipulating the physicochemical profile of nanoparticles, these particles can be distributed to other hepatocytes and, potentially to any other part of the body, depending on the physiological barriers and ultrastructural opportunities provided by the disease process [9].

The large dispersion of red blood cells in vivo and dose-dependent neurotoxicity of oxaliplatin (L-OHP) may restrict its clinical effectiveness. In comparison to L-OHP solution, Nihad Cheraga's group discovered that total platinum in L-OHP long-circulating liposomal plasma had a double exponential pharmacokinetic profile, five times better bioavailability, and a longer distribution half-life. These findings unequivocally show that long-circulating liposomes can enhance L-OHP's pharmacokinetic profile, increasing its therapeutic efficacy and decreasing its toxicity [10].

3.3. Special Functional Liposomes

3.3.1. Heat-sensitive Liposomes

Human tumor tissues exhibit poor blood circulation and are often accompanied by tissue edema, wThese conditions significantly impair heat dissipation, resulting in a slightly higher temperature in the tumor microenvironment compared to that of normal tissues. Studies have shown that tumor cells can be damaged in the temperature range of 42~45 °C, while normal tissues will not be damaged even when the temperature reaches 45 °C due to their superior heat dissipation capabilities. Thus, hyperthermia not only serves as a conventional tumor treatment but also plays a crucial role in targeted therapy of temperature-sensitive liposomes.

William H. Sauer's team [11] conducted study using a porcine model to enhance radiofrequency ablation by systemic infusion of heat-sensitive liposomes or saline controls, followed by doxorubicin in the right atrium. The geometry of the lesion was measured using voltage mapping techniques immediately after ablation and at 2 weeks post-treatment. The results indicated that after 2 weeks, animals treated with heat-sensitive liposomes showed less regression of damage in the scar area

compared to control animals. In addition, the cardiotoxic effects of heat-sensitive liposomes have become more pronounced over time after higher power and longer duration RF applications. Based on this proof-of-concept study, further investigations could explore potential drugs designed to facilitate the ablation of arrhythmic tissues.

The first heat-activated liposomal drug carrier to enter human clinical trials was hemolytic thermosensitive liposomal doxorubicin [12], this formulation is designed to carry a cytotoxic payload and circulate effectively within the body to allow accumulation at the heated tumor site. Upon thermal activation at the target site, the liposomes release their contents at high concentrations, enabling precise drug delivery and enhanced therapeutic efficacy.

3.3.2. PH-Sensitive Liposomes

The pH at the tumor sites is typically lower than that of normal tissues, ranging approximately from 5.0 to 6.5. This phenomenon is primarily attributed to edema, inflammation, and local acidification processes within the tumor area. In contrast, the pH in the plasma of normal tissue fluid is roughly between 7.0 and 7.4. pH-sensitive liposomes have been developed leveraging this characteristic of tumor site, which can specifically target the tumor site and reduce systemic toxicity. In addition, pH-sensitive liposomes have the characteristics of simple preparation and high safety, which can effectively improve the efficiency of gene transfection.

Kang and Park's study utilized pH-sensitive liposomes to amplify the detection of acetylcholine (ACh) [13]. They examined the effects of pH and ACh content on the reaction by adding pH-sensitive liposomes encapsulated with ferricyanide and acetylcholinesterase (AChE) covalently immobilized on magnetic particles to an ACh-distributed cyclic voltammetry solution. It was discovered that AChE activity was reversible in relation to pH variations between 7 and 5. As a portable, quick, and sensitive way to measure ACh concentrations, the technique created in this work is therefore viable.

In order to increase cytotoxicity, Alrbyawi et al. studied the administration of daunorubicin (DNR) via a pH-sensitive liposome system in the B16-BL6 melanoma cell line [14]. For this study, CL was a component of the lipid bilayer that encapsulated DNR in liposomes. According to the results, DNR was able to diffuse more readily into cancer cells because pH-sensitive liposomes altered the physical properties of the plasma membrane. On B16-BL6 cell lines, pH-sensitive liposomes exhibited much greater cytotoxicity and DNR cell uptake effects than liposomes that resembled daunorubicin® and free DNR. This formulation is therefore expected to be a possible medication delivery technique for melanoma treatment.

3.3.3. Ligand Liposomes

Ligand-directed liposomes enable active targeting of tumor cells or tumor-associated stromal cells through surface-linked ligands, thereby increasing selectivity for drug delivery. However, the translational application of this approach in clinical practice is still limited [15].

Paclitaxel-based chemotherapy is a cornerstone treatment for lung cancer, but its systemic toxicity restricts its widespread use. Tianchuanzhu's team [16] designed a hybrid nanovesicle called Lip-CExo@PTX for immunochemotherapy of lung cancer by fusing bispecific CAR-T cell-derived exosomes targeting mesothelin and programmed death-ligand-1 with lung-targeted liposomes. Over 95% of intravenous injected Lip-CExo@PTX accumulates in lung tissue because of liposomes' ability to target the lung. Furthermore, PTX and cytotoxic particles within Lip-CExo@PTX are further delivered into targeted mesothelin-positive tumors with the help of anti-targeted mesothelin single-chain variable fragments, extending the survival period of tumor-bearing mice in the CT-26 metastatic lung cancer model. By continually delivering PTX to tumor cells by continuous targeted

delivery, Lip-CExo@PTX may therefore present a promising approach for lung cancer immunochemotherapy, consequently increasing anti-tumor effects.

Monotherapy is often insufficient to effectively inhibit tumor development and metastasis due to severe systemic toxicity and drug resistance, making combination therapy a more effective strategy. Wang F's team [17] has developed a novel two-ligand-modified curcumin and conristatin A-4 phosphate co-loaded glycyrrhetic acid and galactose two-ligand modified liposomes (CUCA/GA&Gal-Lip) for the first time for anti-liver cancer treatment. Curcumin and Conristatin A-4 phosphate can inhibit tumor angiogenesis and metastasis by down-regulating the expression of vascular endothelial growth factor and vascular endothelial growth factor receptor 2, respectively. Moreover GA&Gal-Lip can improve anti-tumor effects through GA/Gal-mediated active targeted delivery, demonstrating excellent anti-liver cancer efficacy.

4. Application of Liposomes in the Field of Anti-Tumor

Injectable drug delivery technologies have advanced significantly in the treatment of cancer during the last few decades. Numerous new delivery systems, including as liposomes, lipid nanoparticles (LNPs), and other nanoparticles with or without macromolecular conjugates, have been made possible by these developments [18]. LNP-based drug delivery systems have shown numerous noteworthy benefits over conventional liposomal and chemotherapeutic medicines, including reduced toxicity, precise control and prolonged release of antineoplastic medications, and superior biocompatibility.

4.1. Breast Cancer

Breast cancer is marked by high expression of estrogen receptors and the involvement of multiple key signaling pathways, including MAPK, HER2/neu, PI3K/Akt, and epidermal growth factor receptor (EGFR)/vascular endothelial growth factor receptor (VEGFR). These pathways can be actively targeted by modified liposomes. In recent years, significant clinical progress has been achieved in liposome-supported cancer chemoimmunotherapy.

Resveratrol (RES) is a naturally occurring compound with potent anticancer properties. However, its clinical application is limited by its low water solubility, poor stability, and low bioavailability. Y. N. Zhao and Y. N. Cao, Ph.D., found that loading RES into peptides and Sucrose liposomes (PSLs) significantly improved their physicochemical properties and could be used to effectively treat breast cancer using liposome-mediated RES delivery [19]. The PSL (complex: PSL@RES) loaded with RES exhibited good stability, high encapsulation efficiency, and achieved sustained release of RES in vitro, effectively inhibiting the growth of cancer cells. Importantly, encapsulating of RES in peptide liposomes significantly reduced its toxicity to mice.

About 15–25% of all occurrences of breast cancer are triple-negative breast cancer (TNBC), which is extremely aggressive, resistant to medication, and linked to a poor prognosis. For the treatment of breast cancers, Duopeng An's group [20] creatively integrated long-acting interleukin 21 (IL-21) with the apolipoprotein A1-modified doxorubicin liposomes (ApoA1-lip/Dox) drug delivery system. While lowering ApoA1-lip/Dox's toxicity, this combination dramatically increased tumor-infiltrating lymphocytes and showed noticeably better anti-tumor activity. In the treatment of TNBC, this tactic offers a fresh way to improve anti-tumor responses and reduce toxicity.

4.2. Lung Cancer

Lung cancer is one of the most common and aggressive cancers in the world, with one of the highest mortality rates among both men and women, posing a significant threat to the lives of over 1.6 million people worldwide. In recent years, lipid-based nanocarriers have shown great potential in the

treatment of lung cancer. Studies have shown that such nanocarriers can effectively stabilize therapeutic compounds, overcome barriers to cell and tissue absorption, and significantly improve the efficiency of drug delivery to specific target regions within the body [21].

In a review article, Leila Glolami noted that liposomal structures exhibit significant tumor suppressive effects in both in vitro and in vivo studies [22]. For instance, Cheng et al. documented that doxorubicin-carrying liposomes modified with GE-11 exhibited a 2.2-fold greater buildup and persistence in tumor tissues relative to non-modified liposomes. In a separate investigation, a liposomal curcumin dry powder inhaler was employed to address rat lung cancer as an animal model, showing superior anti-cancer effectiveness compared to gemcitabine based on pathological findings and cancer biomarker levels. Lu et al. explored the combination of liposomal paclitaxel with systemic chemotherapy (carboplatin and gemcitabine) and verified its manageable toxicity profile. Furthermore, Song et al. developed a multifunctional targeted liposome for non-small cell lung cancer therapy, altering the liposome surface with octreotide, proving that it can lower PI3K, MMP-2, MMP-9, VE-cadherin, and FAK levels, while activating caspase 3, which displayed notable anti-tumor effects in animal studies, offering an innovative approach for treating non-small cell lung cancer.

4.3. Glioma

Gliomas are among the most aggressive types of cancer, with patients typically surviving only 12 to 15 months after initial diagnosis. The limited penetration of anticancer agents through the blood-brain tumor barrier poses significant challenges for conventional chemotherapy in delivering therapeutic doses of common agents. Among various nanopreparations, liposomes are considered the most promising carriers for the glioma treatment due to their unique targeting and biocompatibility [23].

The external factors influencing liposomal cell uptake in glioma cells are not well understood. Heparin and its analogues are commonly used in glioma patients to reduce the risk of thromboembolic events. Thomas S. van Solinge et al. [24] found for the first time that heparin significantly inhibited liposome uptake by U87 and GL261 glioma cells, with this inhibition was closely related to the presence of fetal bovine serum in the medium. This finding provides an important basis for understanding the potential impact of heparin in glioma treatment.

Using ginsenoside Rg3 as the foundation, the research team under the direction of Ying Zhu [25] worked to create a multifunctional liposome system (Ginsenoside Rg3-Liposomal system, Rg3-LPs). Research results showed that Rg3-LPs might significantly increase cell uptake and the capacity to penetrate glioblastoma spheroids in vitro when compared to regular cholesterol liposomes (C-LPs). Additionally, it might improve the glioma's active targeting and in vivo tumor spread. Subsequent experiments demonstrated that Rg3-LPs loaded with paclitaxel (Rg3-PTX-LPs) significantly outperformed C-LPs loaded with paclitaxel in their ability to inhibit the proliferation of C6 glioma cells. These results suggest that in drug-delivery liposomes, ginsenoside Rg3 may be a suitable substitute for cholesterol. These results suggest that ginsenoside Rg3 is a good substitute for cholesterol in drug-delivery liposomes and has synergistic effects with loaded anticancer drugs, making it a highly promising multifunctional anti-glioma drug delivery system.

5. Conclusions and Outlook

Liposomes, as an outstanding drug carrier, have demonstrated significant advantages in drug targeting, effectively enhancing therapeutic efficacy and markedly reducing systemic adverse reactions. They also exhibit excellent characteristics in combating drug resistance. However, despite these advantages, the development of liposomes still faces numerous challenges that need to be addressed. For instance, the enhanced permeability and retention (EPR) effect has long been considered the foundation for tumor-targeted drug delivery. Yet, in clinical practice, the actual therapeutic outcomes of nanodrugs

have fallen far short of expectations. These drugs only manage to reduce toxicity to a certain extent, but fail to significantly improve clinical efficacy.

Moreover, the therapeutic effects vary greatly among different types of solid tumors and even within different regions of the same tumor. Additionally, due to the phototoxicity of photosensitizers, patients treated with photodynamic drugs are highly susceptible to adverse reactions such as rashes when exposed to ultraviolet radiation, a problem that cannot be overlooked.

Despite these challenges, the application prospects of liposomes in the field of antitumor therapy remain very broad, with great potential for development and rapid growth. Currently, several liposomal formulations have been successfully marketed in China, including 5-FU multilamellar liposomes, paclitaxel liposomes for injection, amphotericin B liposomes for injection, and doxorubicin liposomes. The successful application of these products has laid a solid foundation for the further development of liposome technology. Looking to the future, we have every reason to believe that with continuous technological advancements and in-depth research, more efficient and safer liposomal formulations will emerge, bringing new breakthroughs and hope to antitumor therapy.

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